Amendments to the Drawings:

Cancel sheet 11 of 11 containing Figs 12 a and 12 b which erroneously appeared in the republication of the application on March 13, 2008, Pub. No. US 2008/0064848.

REMARKS/ARGUMENTS

This amendment is filed in response to the Office Action mailed April 1, 2008 for the above captioned application. Reconsideration of the application as amended in view of the remarks herein is respectfully requested.

It is noted that in the republication of the application on March 13, 2008, an extra sheet of figures (Sheet 11 of 11) which had been canceled in the preliminary amendment was included in the publication. To ensure that this does not appear in the final issued patent, Applicants have included a drawing amendment canceling this sheet.

Although no objection or rejection was made, Claim 122 has been amended so that it is different in scope from claim 121.

Claims 121, 122, 125, 128 and 131 were rejected under 35 USC § 101. An amendment has been made to indicate that the claims refer to an "isolated and/or purified" monoclonal antibody in accordance with the Examiner's suggestion. This amendment is understood to overcome the rejection.

Claims 121, 122, 125, 128 and 131 were rejected as anticipated by WO 91/09137. The Examiner indicates that the claims as written (before this amendment) read on naturally occurring human autoantibodies. However, there is no disclosure of isolated and/or purified human monoclonal antibodies, and therefore the amendment to these claims to address the § 101 rejection is believed to overcome this rejection as well.

Claim 121 has also been amended to include the limitation that the binding partner has the characteristics TSH receptor antibodies present in the serum of patients with hyperthyroid Graves disease with respect to inhibition or stimulation of TSH binding to the TSH receptor.. This limitation is supported in the application as filed, inter alia at Page 4, lines 26-28; Page 5, lines 22-28.

Claim 198 has been added to recite that the binding partner has an affinity for the TSH receptor of at least 10^{10} M^{-1}. This limitation is supported at Page 37, lines19-20. Claim 199 has been added in recite that the binding partner inhibits and/or stimulates the TSH receptor. This amendment is supported on Page 1, lines 12-21 and Page 5, lines 22-28.

Claims 121, 122 and 128 stand rejected as anticipated by Akamizu et al. Akamizu describes the characteristics of two particular antibodies isolated from the lymphocytes of patients with Graves' disease. Applicants respectfully submit that the mere fact that these

antibodies were isolated lymphocytes of the a Graves' disease patient does not mean that they have the characteristics of "TSH receptor autoantibodies present in serum of patients with hyperthyroid Graves disease" as required in claim 121. Furthermore, consideration of the information provided in the reference argues against any claim that they might inherently possess such properties.

The characteristics of the TSH receptor autoantibodies that are characteristics of Graves' disease are described in the specification and are known in the art. These include the ability to inhibit and/or stimulate the receptor, and high affinity for the TSH receptor, such that the inhibition or stimulation occurs at levels of autoantibody found in patient serum. Prior to the present invention, the preparation of a monoclonal antibody with these characteristics was not established, and skepticism about claims to such antibodies was expressed in the art. For example, Rapoport, *Endocrine Reviews* 19(6): 673-716 (1998), particular a Page 698 attached as Ex. A, expressed doubts about the specificity of human TSHR antibodies reported as of that date. Ando et al. *J. Clinical Invest* 110 (111): 1667- 1674 (December 2002) attached as exhibit B notes that early claims to TSHR antibodies are only achieved at high concentrations of the IgG. Sanders et al., *Thyroid* 12(12): 1043- 1050 (2002) (Exhibit C), a publication of the present inventors and their coworkers, also observed that there were not, as of that date, reports of high affinity TSHR MAbs which can act as thyroid stimulators and inhibit TSH binding to the TSHR. In that same issue of *Thyroid*, an independent guest editorial stated that "after initial claims for the isolation of human monoclonals with TSAb activity, it became clear that the biological activity of these was well below what was expected for the high affinity thyroid stimulating autoantiobodies of Graves' patients." (Exhibit D) More recently, Ando et al., *Clinical & Devel. Immunol.* 12(2): 371-143 (2005) (Exhibit E) have also commented in the high concentrations needed to observe activity of the alleged TSHR antibodies observed before the present invention.

Applying these standards to the antibodies described in Akamizu, it is clear that this is not an antibody with characteristics of the autoantibodies found in Graves' disease patients. The Akamizu antibodies are reported to bind to the TSH receptor with an affinity of $8 \times 10^7\ M^{-1}$ (this is the reciprocal of Kd) and $8 \times 10^6\ M^{-1}$, receptively. In contrast, affinities of autoantibodies associated with Graves' disease are order of magnitude greater, or example $5 \times 10^{10}\ M^{-1}$ as reported in the present results section. Further, the Akamizu paper reports that neither of the antibodies inhibited binding of labeled TSH to the receptor. (Page 1599, Col. 2; Page 1600, Col. 1) The Examiner points to one specific result in the Akamizu parer relating to cAMP stimulation, but the paper provides no basis for a comparison of the magnitude of this effect. It is noted that the amount of antibody use cannot be deduced, and that at best it achieved a result comparable to the middle amount of TSH at this concentration, and results not as good as achieved with patient serum (suggesting low activity). In contrast. the antibodies of the present invention are effective at very low concentration (See Fig. 2) and indeed hMAb TSHR1, which exemplifies the claimed

invention is around 3000 times more potent than patient whole serum IgG in terms of both cAMP stimulation of inhibition of TSH binding activity (See Table 8). Thus, this is not evidence that the antibodies of Azamizu had the characteristics of autoantibodies associated with Graves' disease.

Claims 121, 12, 125 and 133 were also rejected as anticipated by Kohn et al. This reference discloses antibodies with thyroid stimulating and thyrotropin binding-inhibitory activity. However, when one compares Figures 1 and 2 of Kohn concerning cAMP stimulating activity it is immediately apparent that these antibodies lack the characteristics of actual Graves' disease autoantibodies. The disclosed monoclonal antibodies are described as similar to the stimulating potency of whole serum IgG. If the antibody were what it is purported to be, however, the stimulating activity should be much higher per mg, since the whole serum IgG is almost entirely IgG unrelated to TSHR autoantibodies. Furthermore, the Kohn paper is one of the papers specifically mentioned in Exhibits B and C as not actually disclosing monoclonal antibodies with the characteristics of autoantibodies in Graves' disease.

With respect to claims 126, 127, 129, 130, 132 and 133, the Examiner asserts that the comparison of the reference to the asserted standard cannot be made based on the information provided, and therefore that the antibodies of Kohn are assumed to meet this standard. Applicants respectfully disagree. As can be seen from Table 5 of the present application, certain numbers of units are associated with certain levels of activity in NIBSC 90/672 assay. By converting from concentration to units/weight the activity in the units set forth in these claims can be determined. In the case of the IgG and the Mab of the invention in Table 5, 92% inhibition is obtained in assay buffer at a concentration of 100 mg/mL, corresponding to 156 units/mL. As reflected in Fig. 4 of Kohn, comparable inhibition is only achieved with one of the tested antibodies, and then not until a concentration of 100 μg/ml. Thus, plainly the activity of the Kohn antibody much less than the activity as set forth in these claims. Thus, the basis for the anticipation rejection is not supported by the reference.

The Examiner also rejected claims 136 and 137 under 35 USC § 103 as obvious over van der Heijden in view of Kohn as evidenced by additional references. The Examiner asserts that van der Heijden teaches antibody fragments but acknowledges that these fragments lack inhibitory activity with respect to TSH binding or stimulatory activity with respect to cAMP production. Thus, these antibodies do not fall within the limitations of the present claims. The examiner then cites Kohn and recites characteristics of the antibodies. As noted above, these antibodies also do not meet the limitations of the claims, and indeed appear to fail by several orders of magnitude to meet the quantitative standard for inhibition as set forth in claim 136 of 30 units per mg. Thus, the combination of the cited references fail to provide suggestion of the claimed invention as set forth in claims 136 and 137, because at best they would provide

alternative methods to make antibodies or fragments lacking in the characteristics of Graves' disease autoantibodies.

Applicants further submit that the difficulties in the art in making such antibodies, as reflected in the attached exhibits must be taken into account in any assessment of obviousness. Indeed, these difficulties had led some researchers in the field to express "doubt that monoclonal antibodies with TSAb activity would exist at all." (Exhibit D). Faced with such apparent skepticism in the art at the time the present invention was made, along with the acknowledgment (Exhibits D and E) that the present inventors have achieved this result, the assertion of obviousness is plainly unfounded.

For the foregoing reasons, Applicants submit that the rejections presented in this office action are in error. Reconsideration and allowance of the elected claims are therefore urged, in addition, non-elected claim 162 drawn to a method of making the monoclonal antibodies of the invention has been amended to contain corresponding limitations. Recombination and consideration of claims 162-167 are therefore also requested.

Respectfully submitted,

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